ELSPAR - asparaginase powder, for solution
Ovation Pharmaceuticals

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ELSPAR safely and effectively. See full prescribing information for ELSPAR.

ELSPAR (asparaginase) powder, for solution for intravenous use
Initial U.S. Approval: 2007

INDICATIONS AND USAGE

Elspar is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) (1.1)

DOSAGE AND ADMINISTRATION

- 6,000 International Units/m2 intramuscularly (IM) or intravenously (IV) three times a week (2.1)
- Reconstitute in volume appropriate for the intended route of administration:

For IM administration, reconstitute in 2 mL (2.3)
For IV administration, reconstitute in 5 mL (2.3)

- For IM administration, limit the volume at a single injection site to 2 mL; if greater than 2 mL, use multiple injection sites (2.2).
- For IV administration, give over ≥ 30 min through side arm of an infusion of Sodium Chloride Injection or Dextrose Injection 5% (D5W) (2.2).
- Use reconstituted Elspar within eight hours (2.3)

DOSAGE FORMS AND STRENGTHS

- 10,000 International Units as lyophilized powder in single-use vial.(3)

CONTRAINDICATIONS

- Serious allergic reactions to Elspar or other Escherichia coli-derived L-asparaginases (4)
- Serious thrombosis with prior L-asparaginase therapy (4)
- Pancreatitis with prior L-asparaginase therapy (4)
- Serious hemorrhagic events with prior L-asparaginase therapy (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and other serious allergic reactions can occur. Observe patients for one hour after administration. Discontinue Elspar in patients with serious allergic reactions. (5.1)
- Serious thrombotic events, including sagittal sinus thrombosis, can occur. Discontinue Elspar® in patients with serious thrombotic events. (5.2)
- Pancreatitis, in some cases fulminant or fatal, can occur. Evaluate patients with abdominal pain for pancreatitis. Discontinue Elspar in patients with pancreatitis. (5.3)
- Glucose intolerance, in some cases irreversible, can occur. Monitor serum glucose. (5.4)
- Coagulopathy can occur. Perform appropriate monitoring. (5.5)

ADVERSE REACTIONS

Most common adverse reactions are allergic reactions (including anaphylaxis), hyperglycemia, pancreatitis, central nervous system (CNS) thrombosis, coagulopathy, hyperbilirubinemia, and elevated transaminases. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Ovation Pharmaceuticals at 1-800-455-1141 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2007

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Elspar is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of Elspar is 6,000 International Units/m^2 intramuscularly (IM) or intravenously (IV) three times a week.

2.2 Instructions for Administration

When Elspar is administered IM, the volume at a single injection site should be limited to 2 mL. If a volume greater than 2 mL is to be administered, two injection sites should be used.
When administered IV, give Elspar over a period of not less than thirty minutes through the side arm of an infusion of Sodium Chloride Injection or Dextrose Injection 5% (D5W).

2.3 Preparation and Handling Precautions

For IM administration, reconstitute Elspar by adding 2 mL Sodium Chloride Injection to the 10,000 unit vial. Withdraw volume of reconstituted Elspar containing calculated dose into sterile syringe.
For IV administration, reconstitute Elspar by adding 5 mL Sterile Water for Injection or Sodium Chloride Injection to the 10,000 unit vial. Withdraw volume of reconstituted Elspar containing calculated dose into sterile syringe.
Use reconstituted Elspar within eight hours
Parenteral drug products should be inspected visually for particulate matter, cloudiness or discoloration prior to administration, whenever solution and container permit. If any of these are present, discard the solution. However, occasionally, a very small number of gelatinous fiber-like particles may develop on standing. Filtration through a 5.0 micron filter during administration will remove the particles with no resultant loss in potency.

3 DOSAGE FORMS AND STRENGTHS

- 10,000 International Units as lyophilized powder in single-use vial.

4 CONTRAINDICATIONS

- Serious allergic reactions to Elspar or other Escherichia coli-derived L-asparaginases
- Serious thrombosis with prior L-asparaginase therapy
- Pancreatitis with prior L-asparaginase therapy
- Serious hemorrhagic events with prior L-asparaginase therapy

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Serious Allergic Reactions

Serious allergic reactions can occur in patients receiving Elspar. The risk of serious allergic reactions is higher in patients with prior exposure to Elspar or other Escherichia coli-derived L-asparaginases. Observe patients for one hour after administration of Elspar in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (for example, epinephrine, oxygen, intravenous steroids, antihistamines). Discontinue Elspar in patients with serious allergic reactions.

5.2 Thrombosis

Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving Elspar. Discontinue Elspar in patients with serious thrombotic events.

5.3 Pancreatitis

Pancreatitis, in some cases fulminant or fatal, can occur in patients receiving Elspar. Evaluate patients with abdominal pain for evidence of pancreatitis. Discontinue Elspar in patients with pancreatitis.

5.4 Glucose Intolerence

Glucose intolerance can occur in patients receiving Elspar. In some cases, glucose intolerance is irreversible. Monitor serum glucose.

5.5 Coagulopathy

Increased prothrombin time, increased partial thromboplastin time, and hypofibrinogenemia can occur in patients receiving Elspar. CNS hemorrhages have been observed. Monitor coagulation parameters at baseline and periodically during and after treatment. Initiate treatment with fresh-frozen plasma to replace coagulation factors in patients with severe or symptomatic coagulopathy.

6 ADVERSE REACTIONS

The following serious adverse reactions occur with Elspar treatment [see **Warnings and Precautions (5)**]:

- Anaphylaxis and serious allergic reactions
- Serious thrombosis
- Pancreatitis
- Glucose intolerance
- Coagulopathy

The most common adverse reactions with Elspar are allergic reactions (including anaphylaxis), hyperglycemia, pancreatitis, central nervous system (CNS) thrombosis, coagulopathy, hyperbilirubinemia, and elevated transaminases.

6.1 Clinical Trials and Post-Marketing Experience

The adverse reactions included in this section were identified in single-arm clinical trials in which Elspar was administered as part of a multi-agent regimen or from spontaneous post-marketing reports or published literature.

Because these adverse events were identified in clinical trials that were not designed to isolate the adverse effects of Elspar or were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious Adverse Reactions

Anaphylaxis and serious allergic reactions. Allergic reactions have occurred with the first dose and with subsequent doses of Elspar. The risk of serious allergic reactions appears to be higher in patients with prior exposure to Elspar or other Escherichia coli-derived L-asparaginases.

Serious thrombosis, including sagittal sinus thrombosis

Pancreatitis, in some cases fulminant or fatal

Glucose intolerance, in some cases irreversible

Coagulopathy, including increased prothrombin time, increased partial thromboplastin time, and decreased fibrinogen, protein C, protein S and antithrombin III. CNS hemorrhages have been reported.

Central Nervous System effects including coma, seizures, and hallucinations.

Common Adverse Reactions

Azotemia, liver function abnormalities, including hyperbilirubinemia, and elevated transaminases.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity, defined as development of binding and/or neutralizing antibodies to the product.

Elspar is a bacterial protein and can elicit antibodies in patients treated with the drug. In 2 prospectively designed clinical trials (N=59 and 24), approximately one quarter of the patients developed antibodies that bound to Elspar as measured by enzyme-linked immunosorbent assays (ELISA).[1,2] Clinical hypersensitivity reactions to Elspar in studies were common ranging from 32.5%[3] to 75%.[1] In these studies, concomitant medications and dosing schedules varied. Patients with hypersensitivity reactions were more likely to have antibodies than those without hypersensitivity reactions.[1] Hypersensitivity reactions have been associated with increased clearance of Elspar.[4] Incidence of antibody formation was lower upon first administration of Elspar than second administration.[1,2] The frequency of antibody formation in adults relative to children is unknown. There is insufficient information to comment on neutralizing antibodies; however, higher levels of antibody correlated with a decrease in asparaginase activity.[2]

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications and underlying disease. Therefore, comparison of the incidence of antibodies to Elspar with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal drug interaction studies between Elspar and other drugs have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. In mice and rats Elspar has been shown to retard the weight gain of mothers and fetuses when given in doses of more than 1000 International Units/kg (approximately equivalent to the recommended human dose, when adjusted for total body surface area). Resorptions, gross abnormalities and skeletal abnormalities were observed. The intravenous administration of 50 or 100 International Units/kg (approximately equivalent to 10 to 20% of the recommended human dose, when adjusted for total body surface area) to pregnant rabbits on Day 8 and 9 of gestation resulted in dose dependent embryotoxicity and gross abnormalities. There are no adequate and well-controlled studies in pregnant women. Elspar should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Elspar is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ELSPAR, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

[See **Clinical Studies (14.1)**]

8.5 Geriatric Use

Clinical studies of Elspar did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Elspar (asparaginase) contains the enzyme L-asparagine amidohydrolase, type EC-2, derived from Escherichia coli. Elspar activity is expressed in terms of International Units according to the recommendation of the International Union of Biochemistry. One International Unit of asparaginase is defined as that amount of enzyme required to generate 1 μmol of ammonia per minute at pH 7.3 and 37°C. The specific activity of Elspar is at least 225 International Units per milligram of protein.

Elspar is provided as a sterile, white lyophilized plug or powder. Each vial contains 10,000 International Units of asparaginase and 80 mg of mannitol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of Elspar is thought to be based on selective killing of leukemic cells due to depletion of plasma asparagine. Some leukemic cells are unable to synthesize asparagine due to a lack of asparagine synthetase and are dependent on an exogenous source of asparagine for survival. Depletion of asparagine, which results from treatment with the enzyme L-asparaginase, kills the leukemic cells. Normal cells, however, are less affected by the depletion due to their ability to synthesize asparagine.

12.2 Pharmacodynamics

The relationship between asparaginase activity and asparagine levels has been studied in clinical trials. In previously untreated, standard-risk ALL patients treated with native asparaginase in whom plasma enzyme activity was greater than 0.1 International Units/mL, plasma asparagine levels decreased from a pretreatment average level of 41 μM to less than 3 μM. In this study, cerebrospinal fluid asparagine levels in patients treated with asparaginase decreased from 2.8 μM (pretreatment) to 1.0 μM and 0.3 μM at day 7 and day 28 of induction, respectively.[2]

12.3 Pharmacokinetics

In a study[5] in patients with metastatic cancer and leukemia, daily intravenous administration of L-asparaginase resulted in a cumulative increase in plasma levels. Plasma half-life varied from 8 to 30 hours. Apparent volume of distribution was slightly greater than the plasma volume. Asparaginase levels in cerebrospinal fluid were less than 1% of concurrent plasma levels.

In a study[6] in which patients with leukemia and metastatic cancer received intramuscular L-asparaginase, peak plasma levels of asparaginase were reached 14 to 24 hours after dosing. Plasma half-life was 34 to 49 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

No long-term carcinogenicity studies in animals have been performed with Elspar.

No relevant studies addressing mutagenic potential have been conducted. Elspar did not exhibit a mutagenic effect when tested against *Salmonella typhimurium* strains in the Ames assay.

No studies have been performed on impairment of fertility.

13.2 Animal Toxicology

Edema and necrosis of pancreatic islets were observed in rabbits following a single, intravenous injection of 12,500 to 50,000 International Units Elspar/kg (approximately equivalent to 25 to 100-fold the recommended human dose, when adjusted for total body surface area). These changes were not reflective of pancreatitis, and were not observed in rabbits following a single intravenous injection of 1000 International Units/kg (approximately equivalent to two times the recommended human dose, when adjusted for total body surface area).

14 CLINICAL STUDIES

Elspar was evaluated in an open-label, multi-center, single-arm study in which 823 patients less than 16 years of age with previously untreated acute lymphoblastic or acute undifferentiated leukemia received Elspar as a component of multi-agent chemotherapy for induction of first remission. Elspar was administered at a dose of 6,000 International Units/m^2 intramuscularly 3 times a week for a total of 9 doses.[7] Of 815 evaluable patients, 758 (93%) achieved a complete remission. In a previous study, in a similar patient population, which utilized an initial induction chemotherapy regimen containing the same agents without Elspar, 429 of 499 (86%) patients achieved a complete remission.

15 REFERENCES

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7. Ortega, J.A.; Nesbit, M.E.; Donaldson, M.H.; Hittle, R.E.; Weiner, J.; Karon, M.; Hammond, D.: L-asparaginase, vincristine and prednisone for induction of first remission in acute lymphocytic leukemia, Cancer Research *37:* 535-540, Feb. 1977.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dosage Form

NDC 67386-411-51

10,000 International Units as lyophilized powder in single dose vial individually packaged in a carton.

Storage and Handling

Keep vials refrigerated at 2-8°C (36-46°F).

Elspar does not contain a preservative. Store unused, reconstituted solution at 2-8°C (36-46°C) and discard after eight hours, or sooner if it becomes cloudy.

17 PATIENT COUNSELING INFORMATION

17.1 Serious Allergic Reactions

Patients should be informed of the possibility of serious allergic reactions, including anaphylaxis, and advised to immediately report any swellings or difficulty breathing.

17.2 Thrombosis

Patients should be advised to immediately report any severe headache. Arm or leg swelling, acute shortness of breath, and chest pain also should be reported immediately.

17.3 Pancreatitis
Patients should be advised to immediately report any severe abdominal pain.

17.4 Glucose Intolerance
Patients should be advised to report excessive thirst or any increase in the volume or frequency of urination.
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